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14. ABSTRACT
This is a multicenter, randomized controlled trial to determine whether early ICU rehabilitation, for Burn Intensive Care Unit (BICU) patients requiring mechanical ventilation will decrease hospital length of stay, 50 subjects will be randomized at each of three sites for a total of 150 subjects. The study has completed all regulatory requirements, completed site protocol developments and has begun to enroll patients. Study start up will be completed within the next month with the site initiation visit for Chapel Hill. The goal enrollment minimums are in average of 2.5 patients enrolled per month, per site. 7.5 patients enrolled per month across the study. This study will increase understanding of the effect of rehabilitation on ICU Burn patients through ultrasound and strength assessments of muscles, performed at study entry (ultrasound), ICU & Hospital discharge and at 3,6, and 12 months (ultrasound & strength assessments) post-enrollment. Functional testing with Short Physical Performance Battery (SPPB) and Health Related Quality of Life (HRQoL) testing will determine if standardized early rehab improves functional performance quality of life and employment status. Accomplishments Year #1: Database build, design web entry case report forms, site training, finalized IRB consent forms and began enrollment 3 subjects to date with out-patient follow up 3, 6, and 13 month sessions planned

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Introduction

This project has received funding to conduct a multicenter, randomized controlled trial to determine whether early ICU rehabilitation, for Burn Intensive Care Unit (BICU) patients requiring mechanical ventilation will decrease hospital length of stay. Fifty subjects will be randomized at each of three sites for a total of 150 subjects. Study start up was initiated and all tasks other than UNC-Chapel Hill site initiation have been completed. Subject enrollment has begun. Screening for study subjects is underway at Wake Forest and Washington University. Three study subjects have been enrolled. Three in-person out-patient visits during the first year post-enrollment will be conducted as well as phone follow-up at the end of second and third years post-enrollment. The sites are now committed to increasing enrollment goals above planned - will average of 2.5 patients enrolled per month, per site; 7.5 patients enrolled per month, across the study, to compensate for the time spent on regulatory work prior to subject enrollment.

This study will proceed and allow for greater understanding of the effect of rehabilitation on the pathophysiology of ICU Burn patients. Through ultrasound and strength assessments of muscles, performed at study entry (ultrasound), ICU & Hospital discharge and at 3, 6 and 12 months post-enrollment will determine if Standardized Rehabilitation Therapy (SRT) decreases loss of biceps and quadriceps muscle mass, architecture change and blunts strength loss. The protocol contains functional testing with the Short Physical Performance Battery (SPPB) and Health Related Quality of Life (HRQoL) testing with SF-36 and Burn Specific Health Scale (BSHS-B). These tools will determine if SRT improves functional performance, quality of life and employment status.

Body

Research Study Accomplishments:

The study's detailed electronic Case Report Form was completed. Also, an electronic, secure study database for remote data entry across sites, was designed, developed, tested and validated. Ultrasound image standardization protocol was developed and has been disseminated across study sites. All IRB and HRPO approvals, at all sites, have been completed.

Finalization of subcontracts with Washington University and University of North Carolina at Chapel Hill has been completed. Payments now have been initiated to both subcontract sites. Study site initiation for Wake Forest and Washington University is complete. Chapel Hill site initiation is now planned. Monthly pan-site telephone conferences have been held. These conferences have permitted protocol understanding through practice with case examples. These exercises have facilitated uniformity across study in the implementation of study screening, as well as use of study inclusion and exclusion criteria. These conferences have also allowed for subject safety discussions. Discussion of adverse event reporting has begun and is ongoing.

Patient screening and patient enrollment:
Patient screening commenced and has been ongoing at Wake Forest since May, 2013. Washington University also began screening in earnest July, 2013.

Patient review:
To date, three study subjects have been enrolled. Appropriate timelines were adhered to in regards to study enrollment windows. Appropriate execution of study inclusion and exclusion rules was conducted. Each study subject had an appropriate study IRB consent form, with appropriate dated signatures, obtained prior to randomization. Randomization procedures were engaged and functioned without difficulty.

To date both study arms have been engaged with study subjects. Standardized rehabilitation therapy and usual care were delivered to study subjects to date. Success was achieved in the delivery of multiple intervention arm rehabilitation sessions including delivery of resistance training exercise with Therabands. Blinded exercise physiologists have conducted the strength and functional assessments according to protocol.

There have been no manuscripts to date. Our first planned publication is targeted for the description of the study's standardization of ultrasound images of muscles in a burn population.

Description of plans to augment enrollment:
To date, the investigators have recognized that the timeframe of the study's first year spent on completing all regulatory and contractual obligations has delayed enrollment considerably. To this point in time, study subject enrollment is not aligned with the proposed timelines offered in the grant application. The investigators agree that alternate strategies are to be engaged to enhance study subject enrollment above the enrollment pace proposed in the grant submission.

The specific strategies identified by the investigators are weekend screening of potential study subjects, temporary voluntary withholding of study contract fees to subcontract sites until study subject enrollment at each site achieves enrollment, and the identification of new study sites.

Key Research Accomplishments:

- All IRB and HRPO obligations have been met
- All subcontract sites have working relationships with Wake Forest to receive study payments
- Electronic secure remote entry database is functioning
- Ultrasound muscle imaging protocol has been completed allowing for standardized images across sites
- Study screening was initiated and is ongoing
- Study subject enrollment and randomization has begun and is ongoing
- Intervention sessions are being delivered according to protocol
- Ultrasound images are being obtained
- Strength and Functional Assessments are being obtained
- Plans for augmentation of study subject enrollment has been discussed by investigators with recognition of need to surpass initial proposed enrollment timelines for timely study completion

Reportable Outcomes

There is now a standardized mechanism to teach and obtain study subject muscle ultrasound images within an ICU Burn Patient population. The muscle ultrasound image protocol design will be an important contribution to the community studying burn patients. The report of the protocol has been identified by the investigators to be the first of the planned study manuscripts.

Conclusions:

To date the investigators conclude that the work performed will allow the study hypotheses to be tested sufficiently. These hypotheses are that standardizing rehabilitation for mechanically ventilated burn patients will:

1) shorten hospital length of stay in burn patients with ARF.

2) prevent loss in muscle size and loss of architecture during critical illness of severe burns.

3) improve objective strength, functional measures, and quality of life at 3, 6, 12, 24, and 36 months post-enrollment.

The investigators conclude that the systems built and implemented for this study will allow for the conduct of a multicenter, randomized controlled trial which will determine whether early ICU, standardized rehabilitation therapy for BICU patients requiring mechanical ventilation with blinded strength assessments decreases hospital length of stay. Fifty (50) subjects will be randomized at each of three sites, for a total of 150 subjects.

Although study start up was prolonged, subject enrollment is now active. Three study patients have been enrolled within a 30 day timeframe. The investigators will perform three in-person visits will occur during 1st year post-enrollment and will be followed by phone follow-up at end of 2nd and 3rd years post-enrollment. Enrollment strategies will be engaged to enhance the initial grant's proposal of 2.5 patients enrolled per month, per site; 7.5 patients enrolled per month, across the study.

Ultrasound and strength assessments of muscles have been successfully performed at study entry, ICU & Hospital discharge. These will continue at 3, 6 and 12 months post-enrollment. These observations will be critical for the study to determine if standardized rehabilitation therapy decreases loss of biceps and quadriceps size, architecture change and blunts strength loss.

Lastly, performance of functional testing with the Short Physical Performance Battery (SPPB) and HRQoL testing with SF- 36 and Burn Specific Health Scale (BSHS-B) will determine if SRT improves functional performance, quality of life and employment status.

MUSCLE ULTRASOUND DETERMINATION OF SKELETAL MUSCLE ARCHITECTURE TO PREDICT TIMING OF FUNCTIONAL RECOVERY IN MECHANICALLY VENTILATED-BURN ICU PATIENTS WITH ACUTE RESPIRATORY FAILURE

Background and Significance:

Acute respiratory failure (ARF) is an extremely variable and heterogeneous syndrome that can be defined as an acute cardiopulmonary dysfunction requiring emergent artificial ventilation support. ARF is a common reason for admission to Intensive Care Units (ICU) in the United States (US). In the US, ARF results in 1.1 million of the 4.4 million ICU admissions each year [1, 2]. For patients with ARF, the mortality rate is higher than the general ICU mortality, with estimates ranging from 15-40% depending on the subgroups evaluated [3-6]. In the largest, most recent report on ARF, the in-ICU mortality was 31% and the overall in-hospital mortality rate was 37%[3]. Annually, 500,000 patients die in US ICUs [1], 400,000 with ARF [3]. Despite the high mortality, average hospital length of stay (LOS) for patients is high. In a 2004 cohort of 5000 patients with ARF, the mean ICU LOS was 8 days and hospital LOS was 17 days [3]. ICU patients requiring longer than 5 days of ICU care make up only 20% of the overall number of ICU admissions, although they account for 61% of ICU days[7], with median hospital costs greater than $30,000[8]. These data suggest that an intervention, such as Standardized Rehabilitation Therapy, that may shorten ICU or hospital stay for patients with ARF, may result in significant cost reductions for US healthcare.

Acute Respiratory Failure survivors experience difficulties in function and quality of life for months following hospital discharge:

Most outcomes research regarding acute respiratory failure has examined short-term endpoints such as in-hospital mortality and morbidities, yet the human cost of these illnesses extends well beyond the period of hospitalization. In a large prospective cohort study of 1,075 survivors of acute respiratory failure, at five months post-discharge 48 percent needed help with at least one activity of daily living, and 27 percent reported their quality of life as fair or poor [9]. Twenty-four percent of patients reported needing assistance with more activities of daily living five months post-discharge as compared to pre-hospitalization [9]. Several investigators have reported on the decrease in health-related quality of life in survivors of the acute respiratory distress syndrome (a subset of ARF), [10, 11] but the reasons for this impairment seemed disproportionate to the improvements in objective pulmonary function tests. In one of the most complete follow-up study of survivors of the acute respiratory distress syndrome to date (86 percent with follow-up data at one year), there was a high prevalence of persistent muscle weakness and fatigue [12]. These data illustrate the deleterious effects that acute respiratory failure has on post-hospital patient function and quality of life. They also signal the importance of including measurements of function and quality of life in the study design of an intervention study such as Standardized Rehabilitation Therapy, in order to capture not only the immediate hospital endpoints of LOS, but to more importantly to capture the intervention's effect on post-hospital patient status.

DOD Burn ICU Muscle Ultrasound Image Protocol

ICU Care imposes immobility which contributes to weakness:

Deconditioning may be described as the multiple changes in organ system physiology that are induced by inactivity and reversed by activity [13]. In the clinical setting, acute deconditioning refers to changes that occur within days to a few weeks of a sudden decrease in activity [14, 15]. Concern regarding bedrest in hospitalized patients is not new [16, 17, 18]. In current practice, admission to an ICU implies almost certain imposed immobility, particularly with mechanical ventilation. In numerous reports from zero gravity (NASA) research, the immobilization of healthy subjects, i.e. without an acute illness, induces muscle atrophy mechanisms with resultant weakness in otherwise normal muscles. However, in addition to immobility, in a new ICU weakness paradigm, the weakness seen in patients with ARF results from multiple potential injuries [14, 15, 19, 20]. Another potential injury is the exposure to systemic inflammation. Injury caused by immobility and acute inflammation may be accentuated by ICU medications such as corticosteroids and neuromuscular blockers [21], as well as hyperglycemia [22]. For those patients with ARF who survive mechanical ventilation, there are reports of substantial difficulties with deconditioning, muscle weakness, joint contractures and dyspnea [12, 23, 24], and the most severe forms have become known as critical illness polymyoneuropathies (CIP) [25].

Muscle weakness is an independent risk factor for mortality from ARF and contributes to long-term reductions in physical function in survivors [12, 26, 27]. Muscle wasting that impairs force, power and fatigability is likely a major driver of the reduced physical function in ARF survivors, and evidence suggests muscle wasting is worse in older versus younger patients [28, 29]. Reduced physical activity, brought about by enforced bedrest, contributes to muscle atrophy in these patients. In response to the burden of debilitating muscular impairment, our center and others advocate early mobility of ARF patients in the intensive care unit (ICU). Mobilizing ARF patients leads to meaningful improvements in clinical outcomes including ventilator days, ICU and hospital length of stay [30-33].

The delivery of rehabilitation strategies for acutely ill patients who do require mechanical ventilation is the subject of recent single-center studies [30, 33, 34]. Currently these studies do provide some data that supports the safety and possibly efficacy of early ICU-related rehabilitation within mechanically ventilated patients. These studies have drawn an association between the delivery of early ICU rehabilitation and some improvements in outcomes such as activities of daily living at hospital discharge, hospital length of stay, and hospital readmission within the 12-months following hospital discharge[30,33,34].

Unfortunately, what is not known for this very ill patient population is how to best individualize the early ICU rehabilitation "exercise prescription". The current studies in this area have approached ICU patients with protocol-driven delivery of early rehabilitation therapies. Much of the delivered exercise is based around sitting, standing, and walking. What does not exist is the ability to formulate an exercise prescription to specifically target a documented muscle abnormality. The study of serial muscle ultrasounds, may allow for such future prescriptions to be configured instantly within the ICU setting, based on that day's muscle study.

DOD Burn ICU Muscle Ultrasound Image Protocol

Muscle ultrasounds are non-invasive, quick and reproducible. They provide the opportunity of ICU staff to create a patient-specific exercise prescription based on both functional assessments and importantly the degree of muscle architecture abnormality detected by ultrasound.

Lastly, examination of serial muscle ultrasounds within the population of ICU patients who require mechanical ventilation for acute respiratory failure, will lead to the ability of investigators to link specific baseline comorbidities, drugs, or fluid administrations, to the onset and duration of architectural changes within muscle and correlate ultimately with muscle function.

Early ICU review of muscle architectural changes detected by serial ultrasound imaging may be a new, non-invasive technique to uniquely identify those ICU patients very early in their course, who would otherwise be destined to develop severe functional deficits in the weeks to months following ICU discharge. Early identification of muscle architectural abnormalities is a potential non-invasive tool for diagnosing and tracking ICU patients at highest risk to develop functional deficits. Study of ICU muscle ultrasound images for architectural abnormalities starting early in a patient's ICU course, provides the opportunity to deliver patient and muscle-specific therapies, new patient-centric assessments and therapies that were previously, absolutely unfeasible.

Now, with the possibility of ultrasound detection of early muscle architectural abnormalities, the Rehabilitation Team may not have to wait until days into an ICU stay when the patient gains consciousness, in order to appraise deficits and then initiate specific rehabilitation therapies.

Objectives:

Serial examination of muscle ultrasound images obtained in mechanically ventilated acute respiratory failure burn patients will allow for better understanding of the time course of specific muscles' architectural abnormalities and the resolution of such abnormalities within hospital survivors. With this study, we will be better able to *understand the relationships between the pattern of resolution of the muscle architectural abnormalities within the context of multiple other clinical abnormalities and therapies present and rendered to ICU burn patients.*

This study will serve to construct power analyses for future intervention studies based upon this study's findings regarding the time to resolution of muscle architectural abnormalities within acute respiratory failure burn patients.

Setting:

Study participants will consist of 150 burn patients with ARF admitted to the Intensive Care Units of Wake Forest University, Washington University, and University of North Carolina-Chapel Hill medical centers.

DOD Burn ICU Muscle Ultrasound Image Protocol

Subjects:

Study participants will consist of burn patients with ARF admitted to the Intensive Care Units. A study coordinator will screen newly admitted ICU burn patients for acceptability into the study. Burn patients who meet the entry criteria will be invited to participate.

Muscle Ultrasound:

Each study subject will undergo an ultrasound to examine the size and echogenicity of their muscles. This involves gel applied to the skin and then the ultrasound probe will be placed on the gel, and the entire process takes less than 20 minutes. The muscles studied will include the biceps brachii, abductor digiti minimi, brachialis complex, tibialis anterior, rectus femoris, and diaphragm.

Anticipated Results:

The ultrasound outcome of this grant application will be to investigate the possibility of a relationship between the ultrasound data and functional measurements (length of stay, grip strength, SPPB, simultaneously accounting for severity of illness).

The ultrasound data analysis may allow for a correlation to be drawn between a pattern of ultrasound changes and length of stay. More specifically, correlation will be studied between ultrasound pattern of change and functional limitation at the time of hospital discharge. The correlation may appear as a link between duration of exposure to mechanical ventilation, and prolonged length of stay or lack of improvement in outpatient functional assessments. Alternatively, we may determine that the initial ultrasound pattern is unaffected by ICU or hospital parameters, and does not associate with magnitude of functional assessments). We anticipate that a higher pixel score within the J-Software analysis of the rectus femoris of the dominant leg will be associated with length of ICU and hospital length of stay, and low magnitude of performance in the functional assessments at hospital discharge through out-patient evaluations. These data represent a mechanistic framework for the explanation of the preliminary data's greater magnitude of muscle homogeneity in ultrasound data to acute respiratory failure and ICU stay.

For acute respiratory failure burn patients, an alteration of muscle architecture, depicted as a more homogeneous appearance on ultrasound images, is expected as the ICU stay progresses. We know from the literature that the length of ICU stay is linked more to the severity of illness than the type or etiology of initial insult. We believe that for this study, as performed in other studies of acute respiratory failure, it is appropriate to group all burn patients together, exclusive of the initial etiology of respiratory failure. Within ICU acuity scoring quartiles, it is suspected that the magnitude of abnormality in ultrasound muscle architecture will best correlate with functional impairment and prolonged length of stay.

Potential Limitations of this Study:

Ultrasound muscle analyses are associated with a great deal of inter-subject variability and inter-rater variability. The inherent noise in the ultrasound measurements, despite software and log transformation techniques within the statistical analyses, may still mask any signal of a relationship

between changes in ultrasound-captured muscle architecture. The numbers of burn patients within this application are small and may limit the ability to statistically distinguish a relationship between ultrasound muscle image alteration and functional assessments. There will be inherent difficulties sorting through the assignment of ultrasound data given the variability in acuity levels that make up acute respiratory failure. Numerous baseline measurements have been built into this study's case report form for database collection for this reason to best assess acuity. Analysis of covariance and the use of propensity scoring may help control for variation in baseline differences in severity of illness. These statistical tools will help in the interpretation of the ultrasound. These will be particularly important in associating any relationship between ultrasound data and functional assessments. Alternatively, mechanisms for improvements associated with ultrasound images may have no relationship to severity of illness, length of ICU or hospital stay nor functional assessments. Rather, intra-subject muscle ultrasound image alterations may be exerted through an effect on such factors as body fluid diuresis, improvement in coagulopathic parameters of inflammation or even reduction of sedation needs. Very detailed clinical data collection will help assess for other associated factors if there are no discernible trends in the relationship between intra-subject ultrasound muscle architecture alterations and functional assessments.

Future Directions:

If the ultrasound image data are found to be correlated with functional outcomes, then in subsequent grant proposals we will study potential mechanisms in the setting of observing and intervening with varying levels on exercise, as they relate to subsequent functional outcomes. The subsequent grant application based on these data will continue to focus on mechanisms of muscle-associated outcome improvement, with emphasis on links among severity of illness, ultrasound alterations and functional outcomes.

As mentioned above, this study will allow us to detect correlations between ultrasound data and functional assessments. Importantly, it will also provide data from which sample size calculations can be performed for the next study. The variations in the ultrasound data and functional outcomes will allow us to determine sample sizes for future studies.

If this study produces meaningful trends to support the study's aims, subsequent applications will be supported that will continue these themes within a larger population. Specifically, formats will be used to further study the relationship between intra-subject muscle architectural abnormalities and duration of functional limitations. In a future studies, patient observation and participation in formal rehabilitation with exercises commencing within the ICU will then be anticipated to go beyond discharge from the hospital.

This application will include opportunities to examine hospital survivors in the outpatient setting.

Data Management:

We propose a secure web-based data entry system for data collection and participant tracking, by the use of specific software. The web-based system allows great flexibility in processing data management

tasks. As data are entered and submitted, edit checks are immediately applied. Entered data are inserted directly into central database. The infrastructure will be a Windows server, running Internet Information Server, to integrate database content within the website. Data will be stored in a secure server relational database. With this web infrastructure, data entered into the system are immediately available for review and reporting. Advanced data cleaning processes are invoked automatically on each form submission using a rules engine for form/field level validation rules and initiation of SAS programs for more extensive reviews and analyses. All systems are backed up nightly to disk which are rotated off site several times a month. In addition, changes to the database are always "inserts" and never "updates" so that inadvertent overwriting of valid data cannot occur and a complete record of database activity is maintained. The web-based system will provide the ability to enter and verify eligibility criteria prior to randomization.

Distributed data entry network: Using the proposed web-based system, research personnel will be able to interact with data through a secure website using web forms that mimic paper forms. We will provide a state-of-the-art query resolution system for forms data. The web-based system is more efficient for research staff to manage data edits than older, paper-based edit query systems. It provides an immediate correction to databases, creates a reliable audit trail, and minimizes redundancies. In prior studies, we have developed and deployed models that incorporate complete sets of validation rules (e.g. range and consistency checks) and display invalid data and potential queries on the data entry screen as the form is submitted. Research staff can resolve many queries immediately, comparing the screen to the form, often cleaning the entire database record on the spot. For queries not immediately resolvable, warnings are displayed whenever the data entry screen is recalled.

Data integrity and security: All study data will be stored centrally in our relational database management system. All systems are securely controlled in the Department of Internal Medicine data center, which has limited access through badge access (with direct reporting to the Security office). The data center has environmental controls to monitor power, temperature, humidity, sound levels and triggers for notifying staff and engineering that are on-call 24x7.

Human Subjects Protection:

Subjects will be enrolled from the burn patients who present to the Wake Forest ICUs. No children will be enrolled in this trial.

Surrogate consent will be obtained from the legally authorized representative when the subject is unable to consent on their own behalf. They will have the protocol explained to them, be given the opportunity to ask questions and have all of their questions answered to their satisfaction. Appropriate time will be allowed for them to review the consent form and talk with other family members or friends as needed. No study procedures will take place prior to informed consent being obtained. There will be an ongoing dialog between the study team and the family to allow for withdrawal of the subject at any time if they so choose. At the point that the subject is conscious and coherent, the consent procedure will be repeated and the subject will be given the opportunity to sign themselves.

DOD Burn ICU Muscle Ultrasound Image Protocol

Subjects if able will be the primary source of consent. Whenever possible a family member or person of their choice will be included in the discussion and consent process. If the subject is not able to participate in the consent process due to critical illness or sedation the following procedure will be followed.

The legally authorized representative will be identified and approached for consent. Members of the research team will be introduced. It will be made clear that the research is separate from the potential study subjects' routine clinical care. The Legally Authorized Representative will be invited to a private conference room in the critical care area. If subjects become alert, coherent, and oriented and able to sign consent at some point after surrogate consent was obtained, consent will be re-obtained from them and the same documentation process will occur.

A brief overview of the subject's current condition will be given, the protocol will be reviewed in detail, and the legally authorized representative will be given an opportunity to ask questions. All questions will be answered. The legally authorized representative will be given an opportunity to read the consent form in full; if unable to read, the consent form will be read to them, or another family member or friend who can read will be identified and asked to read it to the legally authorized representative. The legally authorized representative will be offered a period of time to consider the protocol if they so desire prior to signing the consent. A copy of the consent will be given to the legal representative as well as information as to how they can contact the research team with any questions or if they should change their mind about continuing participation.

A note will be placed in study chart noting the individuals present during the conversation and the date and time that consent was obtained. It will be signed by the person obtaining consent as well as co-signed by the PI or Co-Investigator. A copy of the signed consent, stamped with the subject's hospital medical record number, will also be placed in the chart.

Protection Against Risk:

The specific attributes of the Muscle Ultrasound machine allow for this intervention to be applied safely. In our pilot project, there were no episodes of inadvertent tube or line removal. There were no deaths or near deaths during the administration of ultrasound imaging. When testing is performed within the ICU setting, the ICU structure allows for the administration of ultrasound imaging and functional assessments and at the same time continuous clinical assessments of the subject (ICU patient) for signs of hemodynamic or respiratory decline.

The interventions within this study, ultrasound and functional assessments, are to be considered as minimal risk to the study subjects at all time points.

Global subject protection:

Universal precautions are practiced throughout the facility. In the event of an adverse event, medical management will be provided at no expense to the subject by the principal investigator, in accordance with the WFUHS Institutional policy for research-related injury.

DOD Burn ICU Muscle Ultrasound Image Protocol

Subject safety is of the utmost concern to the research team and in the event of a serious adverse event subjects will receive state-of-the-art emergency medical care at a level consistent with the Emergency Department. All serious adverse events will be reportedly to the IRB within a 24 hour time period of notification of the event. All clinical coordinators and physician investigators involved in clinical trials are required to attend (and be certified in) educational programs on the protection of human subjects; the "Human Research Subject Protection Education Program", previously called the "Clinical Research Investigator/Coordinator Certificate Program (CRICC)".

The study subjects within this proposal will initially be critically ill and require mechanical ventilation. They often have underlying serious illnesses. Complications of underlying diseases, complications from the admitting diagnosis as well as complications from general ICU exposure are unfortunately common in this population, aside from any participation in a clinical study. Those conditions present at baseline, or in the opinion of the investigator not felt to be directly study procedure-related will be considered a clinical outcome and not a serious adverse event. Therefore, risks felt to be possibly associated with this study would be hypoxemia during the delivery of the ultrasound imaging or functional assessments, cardiac arrhythmias during the delivery of the protocol, or the loss of a management device such as an endotracheal tube or vascular access. Study subjects, while receiving mechanical ventilation and undergoing the study protocol, will be monitored in the ICU. Study subjects will be monitored continuously, while in the ICU setting. If dysrhythmias or increasing ventilatory demands are noted, the protocol will be stopped and the subject re-assessed to determine whether the patient's condition warrants return to the protocol. Confidentiality is maintained by limiting access to study-related records, and maintaining password protection on all databases.

Confidentiality:

All clinical study data will be held in strict confidence. The data will not be shared with any person involved in the conduct of the study until all patient enrollment in the study has ceased, all enrolled burn patients have completed the study, and final data lock has occurred.

The PI and Co-PIs will be responsible for:

• Review of serious, unexpected adverse events, whether or not thought to be related to the protocol's intervention or procedures.

• Review of clinical data and other related data at unplanned intervals when appropriate or when safety issues occur.

• Ensure that analyses performed are recorded, handled and stored in a way that allows accurate interpretation, verification and reporting of the data.

• Maintain minutes of all study monthly meetings whether in person or via teleconference, including the names of attendees, a summary of the discussion, recommendations and the rationale for recommendations.

• Make recommendations to the Study's Co-PI's, IRB and Office of Research representatives including the following: suspend study enrollment due to safety concerns, recommend changes to the protocol, procedures and/or informed consent document or continue the current study.

Data Safety Plan Procedures

Study safety monitoring schedule:

The Study team including the PI and Co-PIs with study staff will meet monthly until the enrollment is achieved.

The Study's Project Manager will initiate review of 2 study subjects per quarter, randomly chosen who have completed hospitalization. The case report forms and subject file will be reviewed for:

- Compliance with IRB requirements
- Conformance with informed consent requirements
- Verification of source documents
- Investigator compliance
- Missed adverse events

Institutional IRB will provide additional oversight if needed. The results of the Project Manager's review will be presented at the subsequent month's staff meeting. At the monthly staff meeting, we will provide opportunity to discuss new human safety concerns by any of our team. Additionally, we will review each of the new subjects enrolled since the last staff meeting in regards to consent form signature and other compliance concerns (such as when the subject was approached to discuss re-consent).

Minimizing research-associated risk:

The protocol gives specific information about patient safety during research study participation. All study burn patients are monitored electronically during the ICU stay and by a critical care nurse presence as well as the continuation of the study teams' presence during the subsequent stay in the hospital and out-patient visits as the protocol is administered. If study subject's health status decreases during a study session, the session will be ended and the critical care nurse will communicate verbally with the study subject's assigned primary team, as well as a written documentation within the patient's electronic medical record.

Protecting the confidentiality of participant data:

The protocol gives guidelines which we follow to protect the confidentiality of patient data. Confidentiality is maintained by limiting access to study-related records and maintaining password protection on the database. Also, all paper records are kept secure in locked offices and are identified by subject study ID.

DOD Burn ICU Muscle Ultrasound Image Protocol

Procedures for identifying, reviewing, and reporting adverse events and unanticipated problems to the IRB, and Office of Research:

The study protocol is consistent with a low risk intervention given that ultrasound and functional assessments constitute the study protocol. The identification, review and reporting process would begin with the Study's research coordinators one the PI or one of the study CO-PI physicians that a potential safety event has occurred. The physician and study coordinator will review the potential safety event together. Patient records will be reviewed for evidence of risk to the patient. The Physician and Study Coordinator will follow the IRB guidelines in adverse event reporting and if the potential event is deemed to have met the criteria, the event will be reported. The reporting of adverse events will be the primary responsibility of the Study PI and Co-PI physicians in conjunction with the Study's project manager who will notify the IRB and representatives of the Office of Research.

An assessment of external factors or relevant information (i.e., developments in the literature, results of related studies) that may have an impact of the safety of participants or on the ethics for the research study:

Current literature will be monitored monthly and pertinent data from such new literature will be discussed at monthly study meetings.

DOD Burn ICU Muscle Ultrasound Image Protocol

Description of Ultrasound Protocol:

1. Measure all muscles in cross-section
2. Make sure US setting depth is deep enough for each muscle and that it is standardized for each muscle.
3. Keep gain and number of focal zones (one) the same.
4. Change angle of insonation to make sure transducer is perpendicular to bone.
5. Make measurements bilaterally.
6. Tibialis anterior: measure from fibular head to lateral malleolus, place transducer 1/3 the distance distal from the fibular head, make sure transducer is perpendicular to tibia and bone edge is crisp
7. Rectus femoris/vastus intermedius complex: measure distance from superior patella to ASIS, place transducer at halfway point, make sure femur edge is crisp
8. Abductor digiti minimi: measure length of 5^{th} metacarpal and place transducer in middle, make sure metacarpal edge is crisp
9. Biceps/brachialis complex: measure distance from antecubital fossa to acromion, place transducer at halfway point, make sure humerus edge is crisp
10. Diaphragm excursion: find mid clavicular line, at lowest costal margin obtain para-sagittal view(anterior subcostal approach)
11. Diaphragm thickness: anterior axillary line, one intercostal above the" peel away : -8-9^{th} IC. Intercostal view
12. Save images to thumb drive using "export" command in folders organized by subject and then sub folder with "day of study"

DOD Burn ICU Muscle Ultrasound Image Protocol

Study subject identifier **Muscle Depth Gain**	**Day 1** (within 80 hours of admission to the ICU)	**Every 7 Days**	**Hospital Discharge Day**	**First post D/C**	**Second post D/C**
Biceps brachii Right Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Biceps brachii Left Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Abductor digiti minimi Right Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Abductor digiti minimi Left Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Rec femoris/vastus inter Right Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Rec femoris/vastus inter Left Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Tibialis anterior Right Thickness Grayscale mean Grayscale SD SQ Tissue Thickness					
Tibialis anterior Left Thickness					

Grayscale mean Grayscale SD SQ Tissue Thickness					
Diaphragm thickness Right Thickness max Thickness min Grayscale mean max Grayscale SD SQ Tissue Thickness					
Diaphragm thickness Left Thickness max Thickness min Grayscale mean max Grayscale SD SQ Tissue Thickness					
Diaphragm excursion Right					
Diaphragm Excursion left					

Ultrasound machine

A SONOSITE portable ultrasound device with an 18 MHz linear array transducer will be used to obtain muscle images at baseline (within 80 hours of admission to the ICU) and then every 7 days. An additional set of images will be obtained within 48 hours of hospital discharge. The muscles imaged will be the tibialis anterior, rectus femoris, abductor digiti minimi, biceps brachii, brachialis complex, and diaphragm. Each muscle will be imaged in the cross-sectional plane each time it will be assessed except for the diaphragm, which will be imaged in the sagittal plane for thickness. Minimal pressure will be applied to the transducer, and bone landmarks will be used to determine if the transducer is oriented perpendicular to the muscle. Each image will be stored on the hard drive of the ultrasound device and then transferred to Image J (NIH, Bethesda, MD) for analysis.

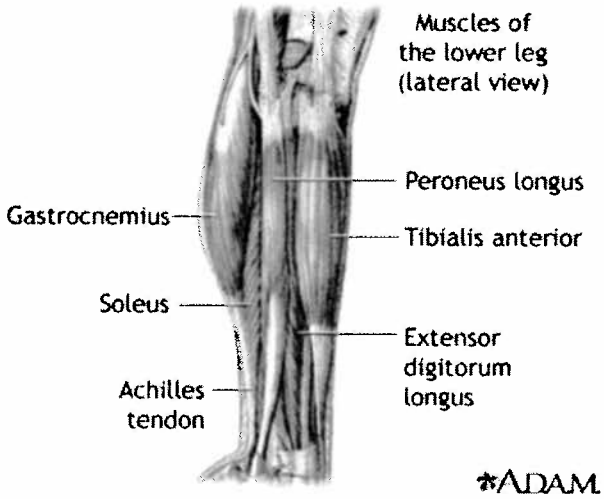
Analyses performed on each image will include measurements of muscle thickness, subcutaneous tissue thickness, mean grayscale values, and standard deviation of the grayscale values. To obtain the grayscale data, Image J will be used and a 2 cm by 2 cm region of interest will be placed over the representative muscle for all muscles except the abductor digiti minimi (a 1 cm by 1cm region of interest will be used) and the diaphragm where 0.5cm by 0.5cm will be used. In grayscale analysis, black is designated 0 and white is 255, with shades of gray in between, and each pixel is assigned a value. This allows calculation of a mean and standard deviation from each region of interest. Care will be taken to only include muscle in the selected region of interest and to avoid including bone, subcutaneous tissue, tendons, other tissues, and artifact.

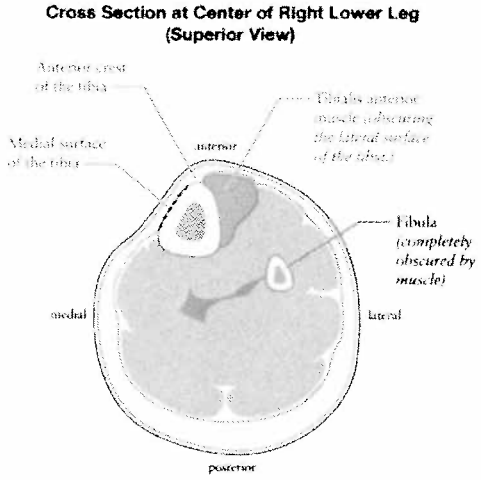
DOD Burn ICU Muscle Ultrasound Image Protocol

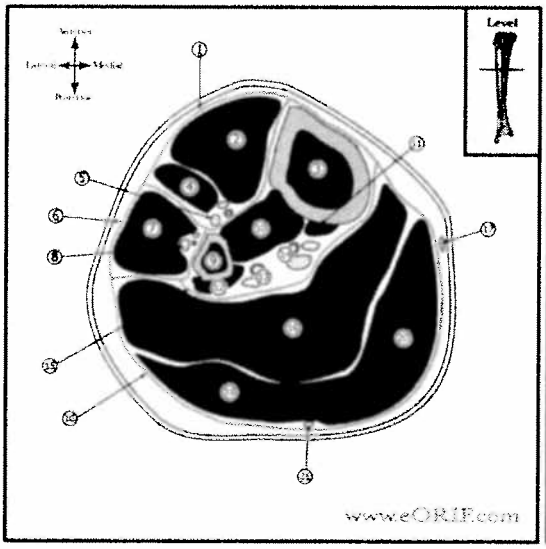
Tibialis anterior

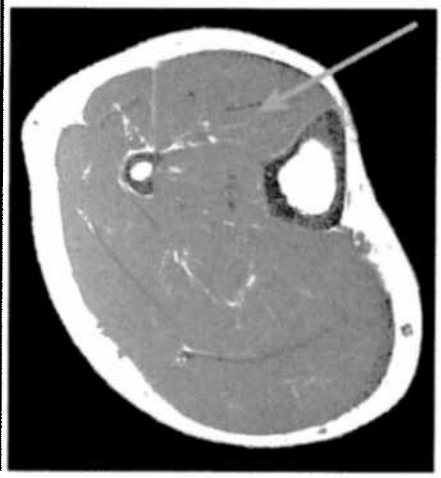
Measure from fibular head to lateral malleolus, place transducer 1/3 the distance distal from the fibular head, make sure transducer is perpendicular to tibia and bone edge is crisp

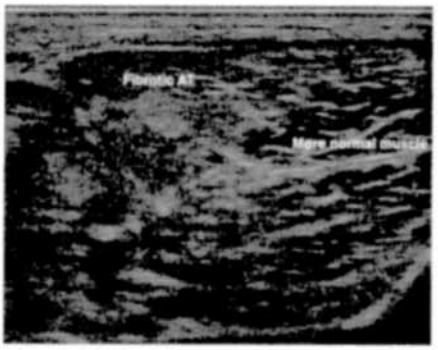
Probe Frequency Depth Gain

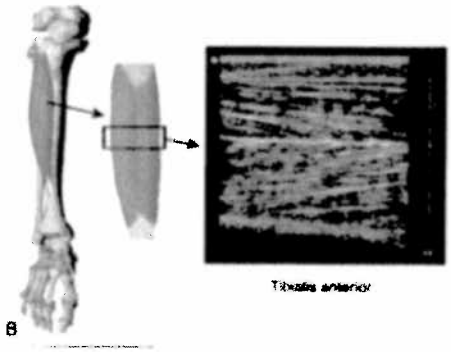












Ultrasound image of the anterior tibialis (*AT*) muscle in a patient who underwent an 11-hour brachial plexus surgery and woke up with footdrop. The muscle has lost the normal heterogeneous, starry night appearance and appears fibrotic, both clinically and electrophysiologically.

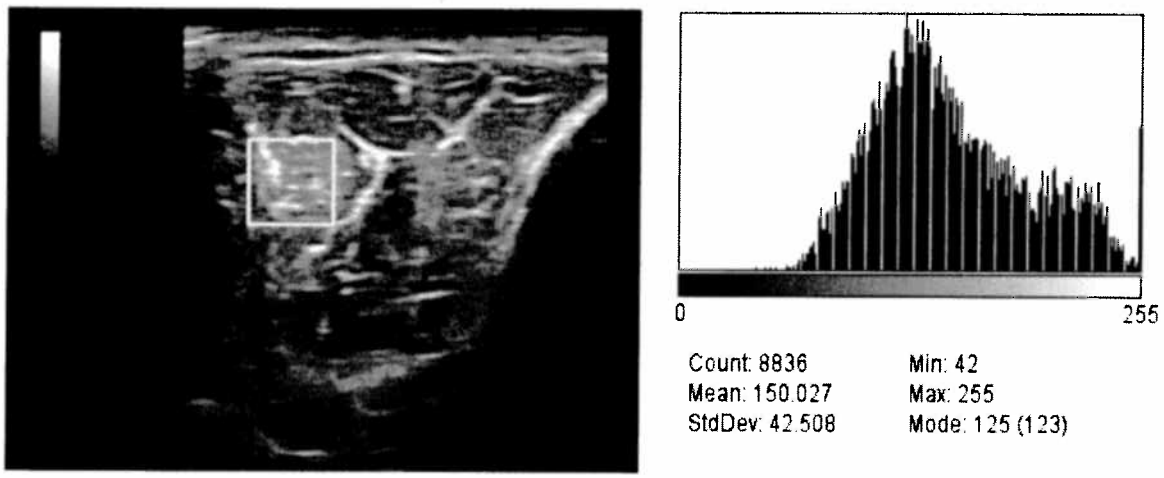


Figure 1. The image on the left shows the tibialis anterior in cross-section. The yellow box is the region of interest, which is placed over a representative section of the tibialis anterior muscle. The image on the right shows the histogram generated from the region of interest in the image on the left. Below the histogram is data generated by Image J, which includes the number of pixels analyzed (8836), the mean grayscale value (150.027), and the grayscale standard deviation (42.508)

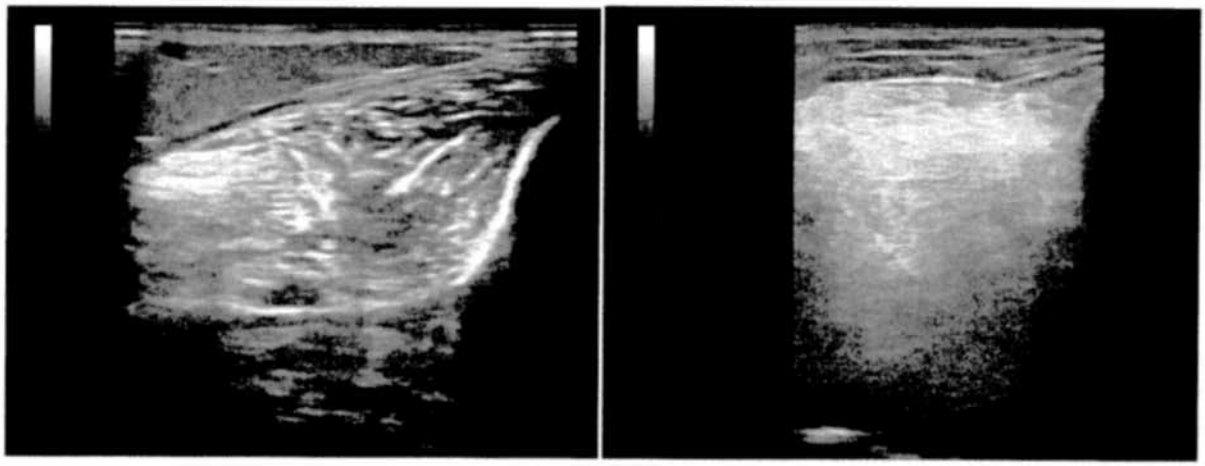


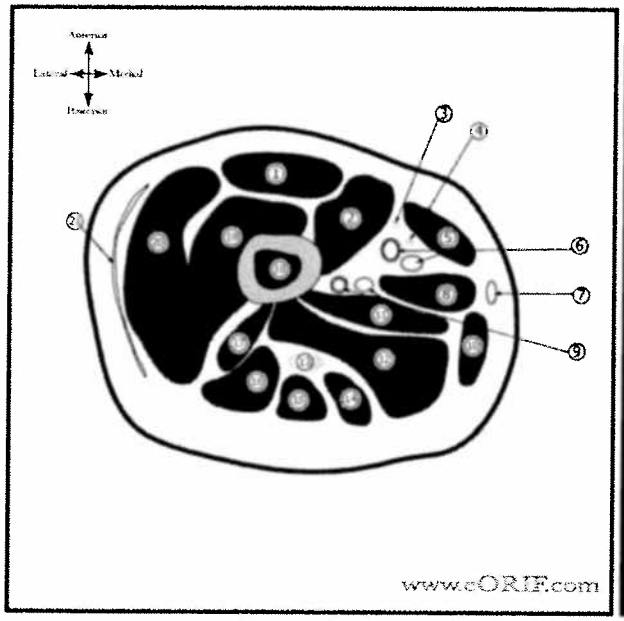
Figure 2. The image on the left shows the tibialis anterior muscle in cross-section at baseline. The image on the right shows the same tibialis anterior muscle after the patient has been in the ICU for 14 days. After the prolonged ICU stay the muscle has lost its normal echotexture and is hyperechoic with a homogeneous, ground-glass appearance.

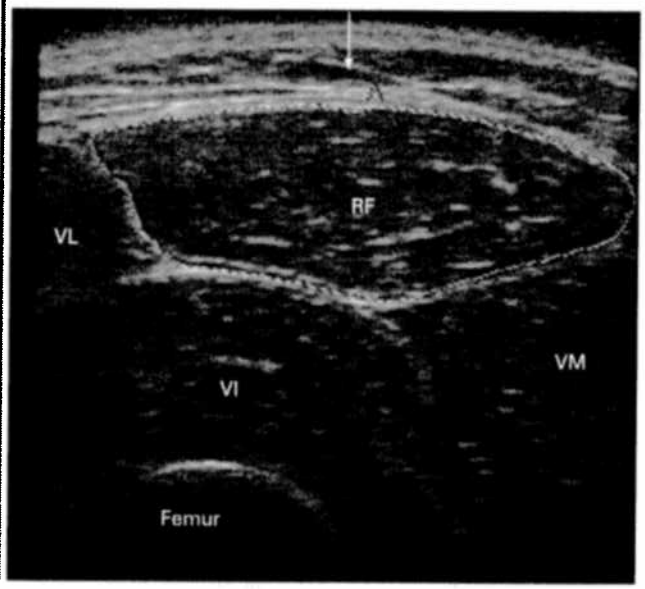
DOD Burn ICU Muscle Ultrasound Image Protocol

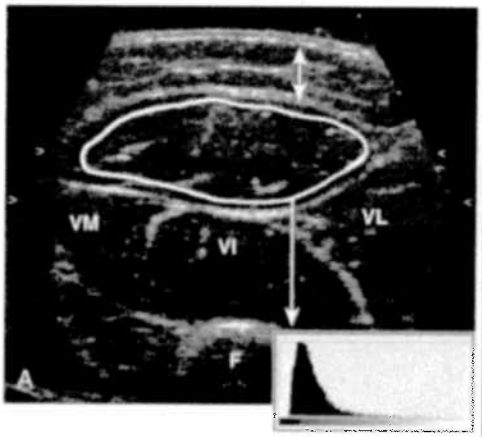
Rectus femoris/vastus intermedius complex

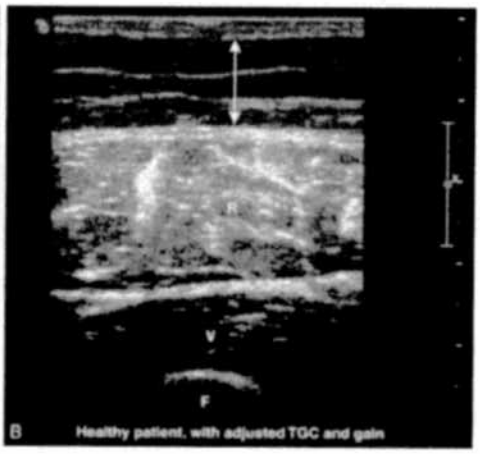
Measure distance from superior patella to ASIS, place transducer at halfway point, make sure femur edge is crisp

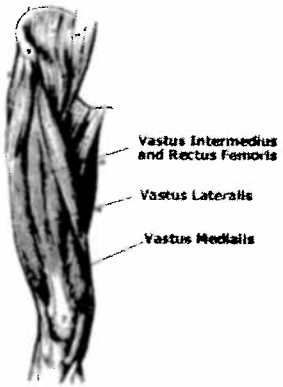
Probe Frequency Depth Gain



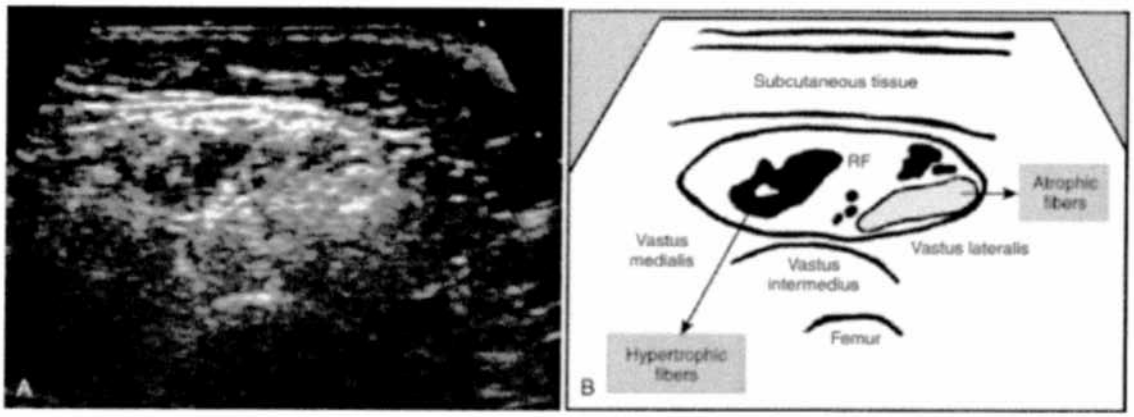




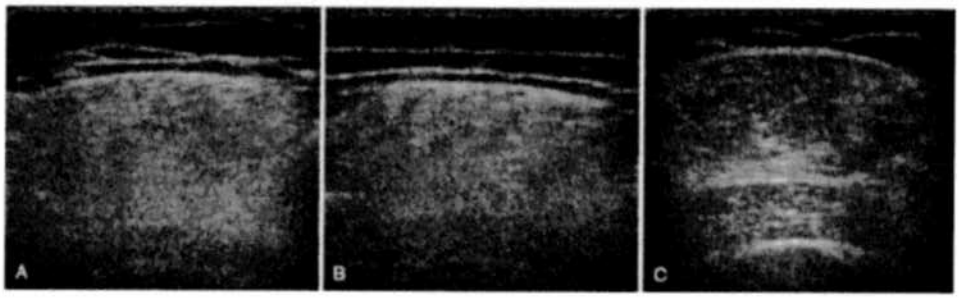




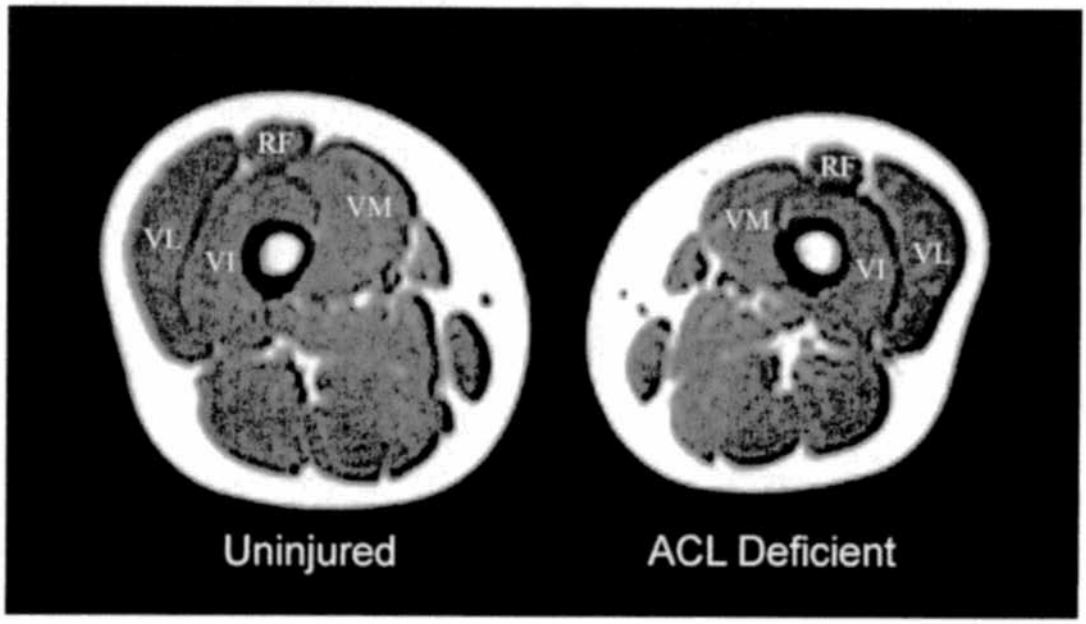
DOD Burn ICU Muscle Ultrasound Image Protocol



R rectus femoris , V vastus Intermedius , F femur



Increased echoes in the rectus femoris are seen on ultrasound of three asymptomatic brothers ages 21 (**A**), 17 (**B**), and 14 (**C**) years with Becker's muscular dystrophy and normal quadriceps strength and function. There is more severe pathology on ultrasound in the older (**A**) than the younger (**C**) brother

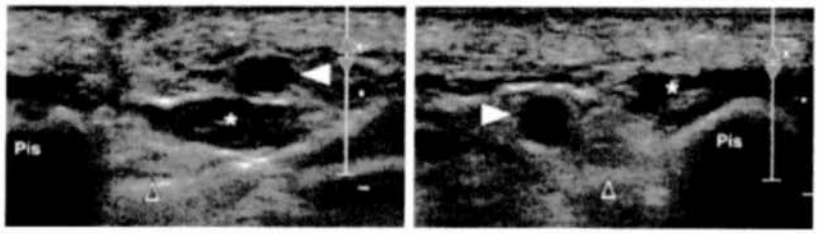


DOD Burn ICU Muscle Ultrasound Image Protocol

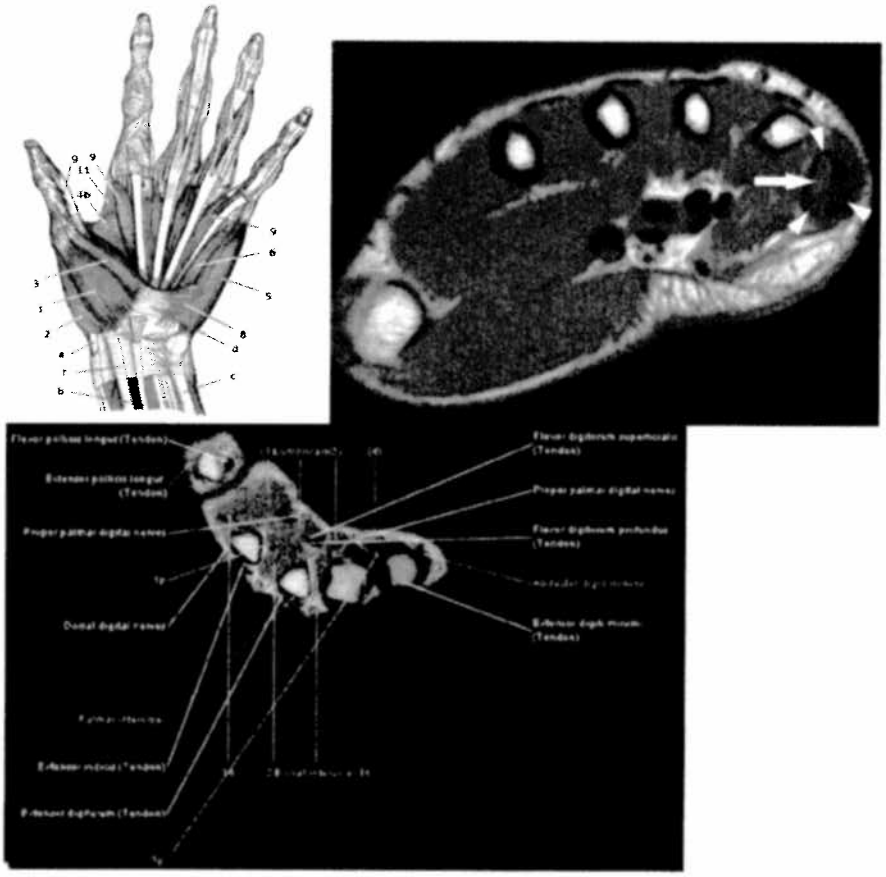
Abductor digiti minimi

Measure length of 5th metacarpal and place transducer in middle; make sure metacarpal edge is crisp

Probe Frequency Depth Gain

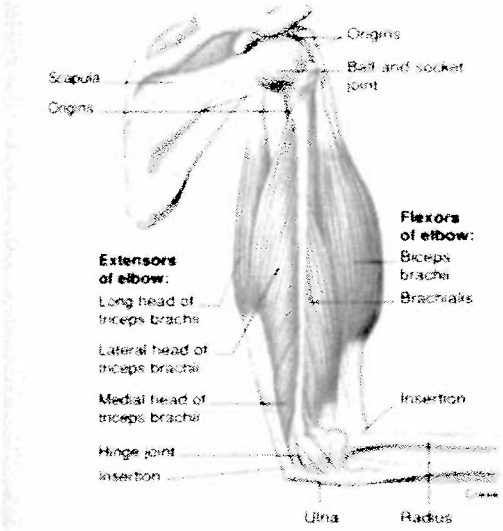


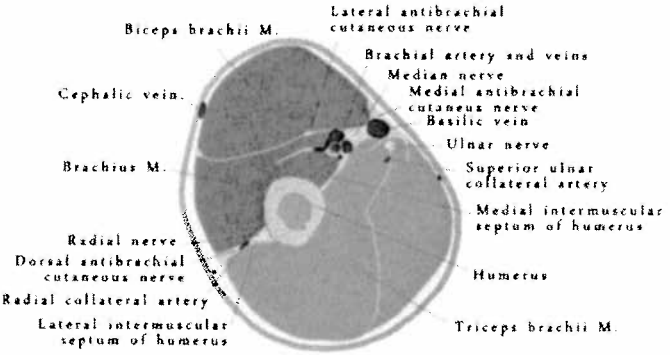
Accessory muscles: 48-year-old woman with left accessory abductor digiti minimi. Transverse sonogram obtained over Guyon's canal shows accessory muscle (*asterisk*) located between ulnar artery (*solid arrowhead*) and nerve (*open arrowhead*). Pis = pisiform. 39-year-old man with right accessory abductor digiti minimi. Transverse sonogram obtained over Guyon's canal shows accessory muscle (*asterisk*) lying inside canal. Muscle is located lateral and palmar to pisiform (Pis). Note ulnar artery (*solid arrowhead*) and nerve (*open arrowhead*).

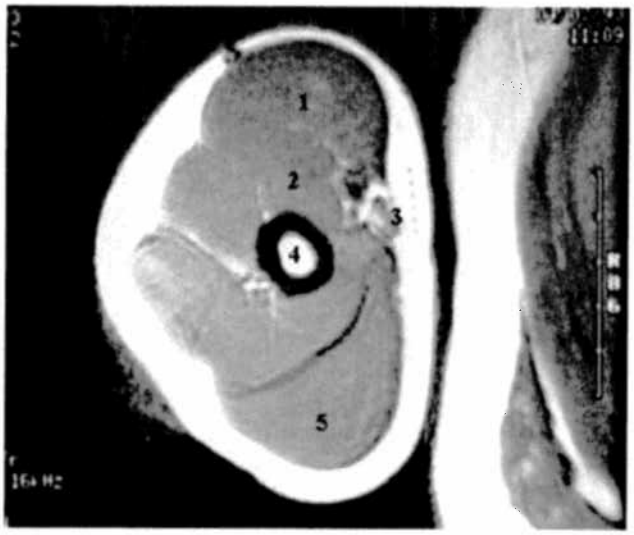


Biceps/brachialis complex

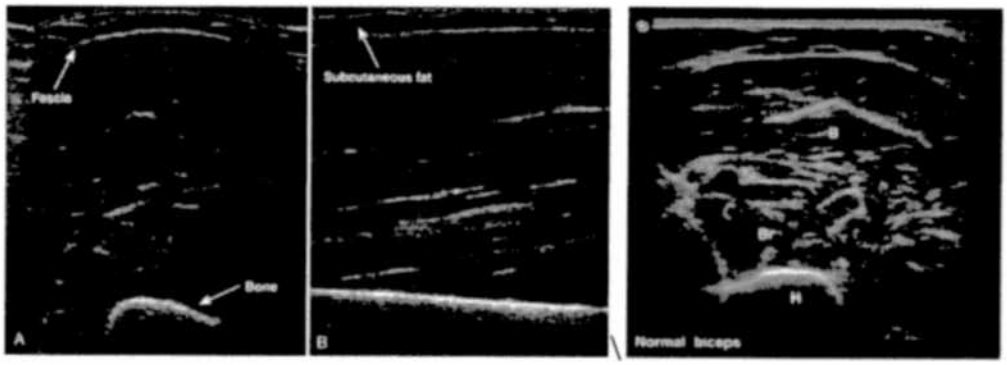
Measure distance from antecubital fossa to acromion, place transducer at halfway point, make sure humerus edge is crisp





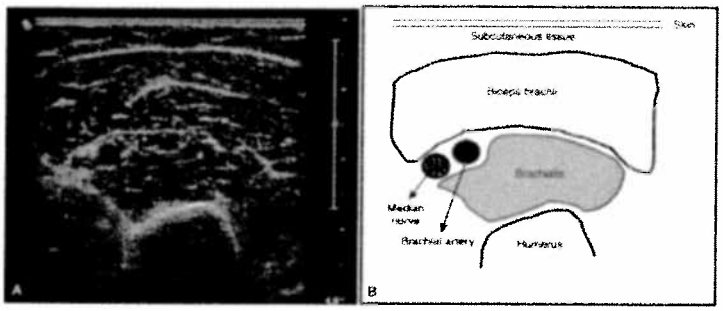


Probe Frequency Depth Gain

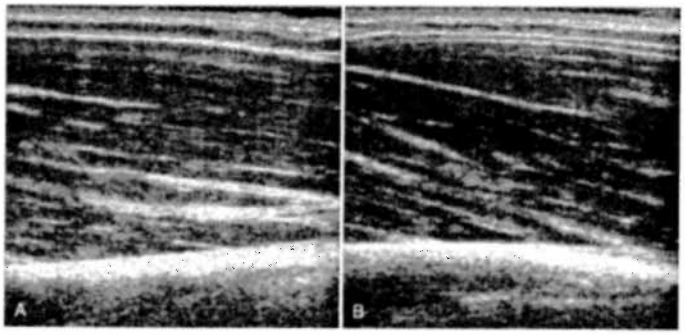


DOD Burn ICU Muscle Ultrasound Image Protocol

Transverse (**A**) and longitudinal (**B**) ultrasound of the normal elbow flexors (biceps brachii and brachialis). The dark muscle is interspersed with bright fibroadipose septa. The bone reflection is very bright and sharply defined. B Biceps brachii , Br Brachialis



A.Normal ultrasound measurement of the biceps brachii muscle and surrounding tissues, measured at two thirds of the distance from the acromion to the antecubital crease of the left arm. **B,** Depicts the different structures schematically



Longitudinal images of the elbow flexors of a healthy 25-year-old man (acquired at system settings optimized for backscatter analysis) show changes in signal intensity with muscle contraction. The mean backscatter is 7 dB brighter in the extended (**A**) compared with the flexed (**B**) arm.

DOD Burn ICU Muscle Ultrasound Image Protocol

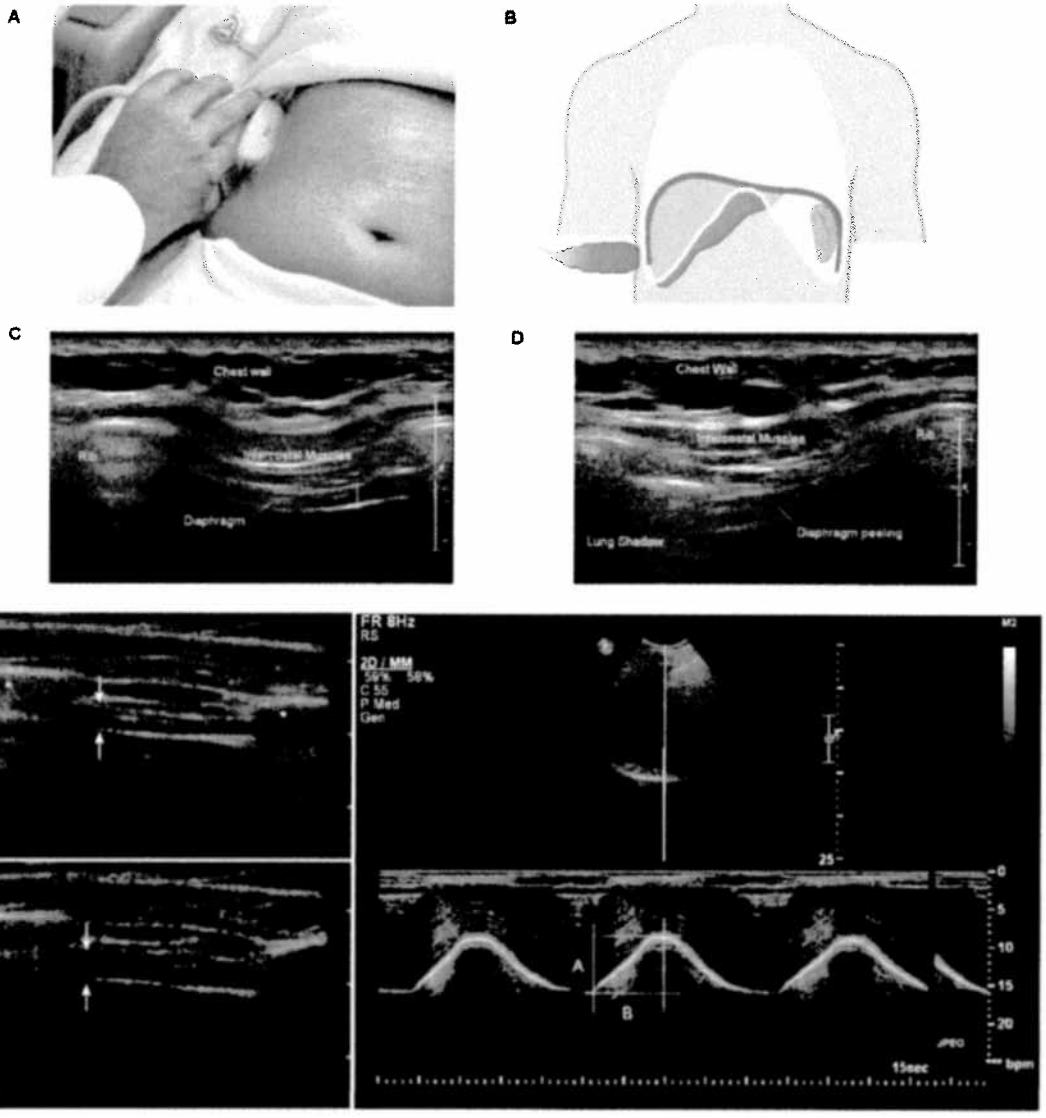
Diaphragm

Thickness: Find anterior axillary line at lowest costal margin, obtain para-sagittal view. Capture diaphragm image one intercostal space above where peeling can be seen, capture image of maximum and minimum thickness on each side with quiet breathing.

Probe Frequency Depth Gain

Excursion : Anterior mid clavicular line

Probe Frequency Depth Gain



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